NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

INTERVENTIONAL PROCEDURES PROGRAMME

Interventional procedure overview of allogeneic pancreatic islet cell transplantation for type 1 diabetes mellitus

Type 1 diabetes mellitus is a condition that occurs when the body does not produce enough insulin (a substance that helps control sugar balance in the body). It is usually treatable with insulin injections, but people with type 1 diabetes mellitus have an increased risk of other health problems, such heart disease. Allogeneic pancreatic islet cell transplantation involves the removal of cells called islet cells, which are responsible for the production of insulin, from human donors. These cells are inserted into the patient's liver to restart insulin production within the body. However, patients who have this procedure will need to take medications to help their bodies' immune system to accept the cells.

Introduction

This overview has been prepared to assist members of the Interventional Procedures Advisory Committee (IPAC) in making recommendations about the safety and efficacy of an interventional procedure. It is based on a rapid review of the medical literature and specialist opinion. It should not be regarded as a definitive assessment of the procedure.

Date prepared

This overview was prepared in August 2007.

Procedure name

- Allogeneic pancreatic islet cell transplantation for type 1 diabetes mellitus

Specialty societies

- British Transplant Society
- British Diabetic Association
- Association of Upper Gastrointestinal Surgeons of Great Britain and Ireland

Description

Indications

Type 1 diabetes mellitus is a disorder in which the pancreas does not secrete sufficient insulin. It is believed to be caused by autoimmune destruction of the islet cells (also known as beta cells). Insulin deficiency leads to an increased level of glucose in the blood (hyperglycaemia) causing diuresis, thirst and dehydration. Insulin deficiency also causes increased fat and protein breakdown and leads to ketone production and weight loss.

Patients with type 1 diabetes require exogenous sources of insulin for the duration of their life. Without medical management, they will develop diabetic ketoacidosis and eventually die. Despite insulin injections, many people with diabetes develop long-term complications such as heart disease, blindness, kidney failure, foot ulcers, peripheral vascular disease and autonomic neuropathy.

Patients with type 1 diabetes are at risk of having hypoglycaemic episodes which occur when blood glucose levels become very low. It can be easily treated by taking glucose but if left untreated it can result in loss of consciousness, seizures, injuries and death.

Type 1 diabetes commonly begins in childhood or adolescence although it can occur at any age.

Current treatment and alternatives

Insulin
Treatment of type 1 diabetes is with multiple daily insulin injections, which deliver a controlled amount of insulin at fixed times in the day. There are different types of insulin with varying times of onset and durations of action.

Insulin can also be administered by continuous subcutaneous infusion, using a pump that is attached to the patient 24 hours a day. It works by delivering a varied dose of fast-acting insulin continually throughout the day and night, at a rate that is pre-set according to the patient's needs. Additional doses can be self-administered after a meal by pressing a button on the pump.

A blood test, that measures glycosated haemoglobin, known as the haemoglobin A1c (HbA1c) test, is used check the patient's average blood glucose control over the past 8 to 12 weeks.

Whole pancreas transplantation
Pancreas transplantation involves the surgical replacement of the patient's own pancreas with that of a cadaveric donor. This has the potential to return the patient's blood glucose level to normal, effectively curing the type 1 diabetes. This procedure is associated with a high complication rate and requires long-term immunosuppression.

Diet
Dietary management is important for reducing the risk of hypoglycaemia or hyperglycaemia after a meal. This includes education about the timing, size, frequency, or composition of meals. Patients and relevant family members should receive a comprehensive diet plan that includes recommendations for daily intake of calories, and the proportion of carbohydrate, fat, and protein in the diet.

What the procedure involves

Allogeneic pancreatic islet cell transplantation involves the infusion of islet cells from one or more dead, or brain dead, human donors into the patient's liver. The donor pancreas is removed and the islet cells are isolated and prepared for transplantation. Before transplantation, the patient is sedated, given a local anaesthetic and antibiotics are administered intravenously. Immunosuppression is initiated and continues long-term after the procedure to prevent rejection of the transplanted cells by the patient's immune system.

A catheter is inserted through the skin into the portal vein of the liver (percutaneous trans-hepatic approach), usually under fluoroscopic guidance, and the islet cells are infused into the liver through the catheter. Alternatively, the portal vein may also be accessed laparoscopically via a tributary such as the mesenteric vein. The patient is given insulin infusions during the procedure to maintain a normal blood glucose level.

Shortly after transplantation, the islet cells begin to produce insulin. Insulin dosing can be reduced or stopped altogether once adequate control of blood sugar level is achieved by the production of insulin from the transplanted islet cells. Patients may require more than one islet infusion over several months before they are able to stop insulin injections and achieve 'insulin independence'.

Efficacy

Insulin requirement
In a registry study of 112 patients, the proportions of patients achieving insulin independence at 6 months and 1 year after transplantation were 67% and 58% respectively. In the patients who remained insulin dependent, there was a mean reduction of 57% in baseline insulin requirements at 6 months and a mean reduction of 69% at 1 year. In this study, 13% (15/112) of patients had complete graft failure.[1]

In a case series of 36 patients, 58% (21/36) achieved insulin independence at any time during the median follow-up of 41 months. However, of these patients, 76% (16/21) were insulin dependent again at 2 years. At 1-year follow-up, 44% (16/36) of patients were insulin independent, 28% (10/36) had partial graft function but remained insulin dependent, and 28% (10/112) had complete graft failure.[2]

In a case series of 65 patients, 68% (44/65) were insulin independent for longer than 1 month after transplantation (median follow-up 36 months). The median duration of insulin independence was 15 months and the mean duration of graft function (measured by C-peptide secretion) was 25 months. Therefore, despite a functioning graft, most patients had to resume taking insulin, although in lower doses than before the procedure.[3]

Hypoglycaemic episodes
In the study of 112 patients, the proportion of patients who experienced a severe hypoglycaemic episode in the year following transplantation was 4.5% compared with 82% in the year prior to transplantation.[1] In the study of 36 patients, there were no hypoglycaemic episodes in all patients who had residual graft function during follow up (ranging from 1 to 12 months).[2] In the study of 65 patients, scores of hypoglycaemic severity and diabetic control were significantly improved compared with baseline for up to 4 years after transplantation.[3]

Quality of life
One study assessed quality of life over 3 years in 23 patients who underwent islet transplantation. One year after completion of the protocol, average scores for all three scales of the Diabetes Quality of Life (DQoL) survey improved significantly from baseline ('satisfaction' with treatment: $p < 0.001$; 'impact' of treatment on quality of life: $p < 0.001$; 'worry' about future impact of diabetes on quality of life: $p = 0.003$). In the Health Status Questionnaire (HSQ) 2.0, which assesses general health-related quality of life, only 1 of 8 scales ('health perception') improved significantly from baseline at most follow-up time points throughout the study.[4] One study reported that fear of hypoglycaemic events fell significantly from baseline 40.2 ± 18.7 points to 53.1 ± 13.8 Following the 1st infusion of islet cells ($p<0.00001$)[9].

Safety

Adverse events
In a case series of 51 patients who underwent islet transplantation, there were nine procedural complications (two cases of portal vein branch thrombosis and seven cases of intra-abdominal hemorrhages).[5]

In a case series of 26 patients, a total of 27 serious adverse events were reported. This study included four patients who underwent a simultaneous islet and kidney transplantation and six patients who under went a simultaneous islet and bone marrow transplantation. 48% (13/27) were considered to be life-threatening and one event (4%) resulted in persistent sequelae or disability. 66% (18/27) of adverse events were related to the immunosuppressive regimen and 15% (4/27) were related to the islet infusion procedure. Procedural complications included bleeding in three patients and subacute cholecystitis and abdominal hernia, each in one patient. Common adverse events included: leukopenia (100%), anaemia (96%), hypophosphatemia (96%), hypercholesterolemia (85%), oral ulceration (77%), upper respiratory infection (69%), and diarrhoea (69%).[6]

In the case series of 112 patients, there were 77 serious adverse events reported to the registry at any time to date. Of these, 22% were considered life-threatening, 58% required hospitalisation and 95% resolved without residual effects. Of these events, 27% were probably or definitely related to the immunosuppressive regimen and 17% to the infusion procedure.[1]

Procedure-related events reported in the study of 65 patients included a major bleed requiring intervention in 15 patients, portal vein thrombosis in 5 patients, gall bladder puncture in 2 patients, and long-term changes consistent with fatty liver disease in 8 patients.[3]

Procedure-related events reported in the study of 36 patients included: intraperitoneal bleeding (7 patients), bile leak requiring laparotomy (1 patient), and partial branch-vein occlusion (2 patients).[2]

A case report described two patients who developed small bowel ulceration that resolved after complete withdrawal of sirolimus, one part of the immunospressive regimen.[7] A second case report described a patient who developed West Nile virus and died 3 years after islet transplantation.[8]

Literature review

Rapid review of literature

The medical literature was searched to identify studies and reviews relevant to allogeneic pancreatic islet cell transplantation for type 1 diabetes mellitus. Searches were conducted via the following databases, covering the period from their commencement to 20/08/07: Medline, PreMedline, EMBASE, Cochrane Library and other databases. Trial registries and the Internet were also searched. No language restriction was applied to the searches. (See appendix C for details of search strategy.)

The following selection criteria (Table 1) were applied to the abstracts identified by the literature search. Where these criteria could not be determined from the abstracts the full paper was retrieved.

Table 1 Inclusion criteria for identification of relevant studies

Characteristic	Criteria
Publication type	Clinical studies were included. Emphasis was placed on identifying good quality studies. Abstracts were excluded where no clinical outcomes were reported, or where the paper was a review, editorial, laboratory or animal study. Conference abstracts were also excluded because of the difficulty of appraising methodology.
Patient	Patients with type 1 diabetes mellitus
Intervention/test	Allogeneic pancreatic islet cell transplantation
Outcome	Articles were retrieved if the abstract contained information relevant to the safety and/or efficacy.
Language	Non-English-language articles were excluded unless they were thought to add substantively to the English-language evidence base.

List of studies included in the overview

This overview is based on six case series[1-6] and two case reports.[7,8]

Other studies that were considered to be relevant to the procedure but were not included in the main extraction table (table 2) have been listed in appendix A.

Existing reviews on this procedure

There were no published systematic reviews with meta-analysis or evidence-based guidelines identified at the time of the literature search.

Related NICE guidance

Below is a list of NICE guidance related to this procedure. Appendix B details the recommendations made in each piece of guidance listed below.

Interventional procedures:

- Pancreatic islet cell transplantation. *NICE Interventional procedure guidance 13* (October 2003). See http://www.nice.org.uk/IPG013 for further information.

Technology appraisals:

- Diabetes (type 1) insulin pump therapy. *NICE Technology appraisal guidance 57* (February 2003). See http://www.nice.org.uk/TA057 for further information.
- Diabetes (types 1 and 2) long-acting insulin analogues. *NICE Technology appraisal guidance 53* (December 2002). See http://www.nice.org.uk/TA057 for further information.

Clinical guidelines:

- Type 1 diabetes. *NICE Clinical guideline 15* (July 2004). See http://www.nice.org.uk/CG015 for further information.

Table 2 Summary of key efficacy and safety findings on allogeneic pancreatic islet cell transplantation for type 1 diabetes mellitus

Abbreviations used: DM, diabetes mellitus; DQoL, diabetes quality of life; HSQ,Health Status Questionnaire; IS, immunosuppressive; MRI, magnetic resonance imaging.

Study details	Key efficacy findings	Key safety findings	Comments
Close N (2007)[1] *Second annual analysis of the collaborative islet transplant registry.* **Case series** North America (19 active islet transplant programmes) Study period: Jan 1999–Dec 2004 **n = 112 patients who had completed at least one follow-up visit since their last infusion (6, 12 or 24 months)** Population: patients with type 1 DM Median age: 41.6 years (range: 23-64 years) Female: > 66% Technique: islet transplantation alone. Various IS regimens (most commonly daclizumab and sirolimus with tacrolimus) given orally. **Follow-up: not stated** Conflict of interest: none stated	**Insulin requirements** • Insulin independence (not defined) at time of publication: 49% (55/112 patients who had completed at least one follow-up visit since their last infusion) • Insulin independence (not defined) at 6 month follow-up (from last infusion): 67% (numbers not reported) • Insulin independence (not defined) at 1-year follow-up (from last infusion): 58% (numbers not reported) Of patients who still required insulin: • 6-month follow-up: 57% mean reduction in the daily amount required compared to baseline • 1-year follow-up: 69% mean reduction in the daily amount required compared with baseline **Graft function** • Complete graft failure (loss of C-peptide function): 13% (15/112) **Hypoglycaemic episodes** Patients who experienced a severe hypoglycaemic episode: • 1 year prior to first infusion: 82% (numbers not reported) • 1 month after first infusion: 2.5% (numbers not reported) • 1–5 months after first infusion: 0% (numbers not reported) • 6–12 months after last infusion: 2% (2 patients)	**Adverse events within 1 year of first infusion** • Patients who experienced ≥ 1 adverse event: 74% (61/83) • Patients who experienced ≥ 1 serious adverse event: 36% (30/83) Number of adverse events (n = 235) probably or definitely related to: • IS regimen: 34% • Infusion procedure: 15% Number of serious adverse events (n = 52) probably or definitely related to: • IS regimen: 29% • Infusion procedure: 23% **Serious adverse events reported to the Registry (at any time to date; n = 77)** • Those considered life-threatening: 22% (17/77) • Those requiring hospitalisation: 58% (45/77) • Resolved without residual effects: 95% (73/77) • Most events related to gastrointestinal disorders, blood and lymphatic system disorders and infections. Number of serious adverse events probably or definitely related to: • IS regimen: 27% (numbers not reported) • Infusion procedure: 17% (numbers not reported)	This is the most recent study of results from all centres reporting to the Collaborative Islet Transplant Registry. These results are likely to include some of the same patients as those reported on in the following studies in this table.

Abbreviations used: DM, diabetes mellitus; DQoL, diabetes quality of life; HSQ,Health Status Questionnaire; IS, immunosuppressive; MRI, magnetic resonance imaging.			
Study details	**Key efficacy findings**	**Key safety findings**	**Comments**
Toso (2007) **Non randomised controlled trial** Canada Study period: not statd **n = 265 (99 patients transplant, and 166 matched patients with type 1 diabetes and no transplant)** Population: patients with type 1 DM Median age: 44.3 years (± 9.6) Female: = 56% Technique: islet transplantation alone. Various IS regimens (regimen and route not descriebd). **Follow-up: 36 months maximum** Conflict of interest: none	**Quality of life** General HUI2 scores At 1 month scores in the transplant group were significantly lower (worse) than at baseline 0.75 ± 0.17 Vs 0.81 ± 0.12 ($p<0.05$) For all subsequent follow up points to 36 months the difference was not statistically significant. Following the 1st infusion HFS fell significantly from baseline 40.2 ± 18.7 Vs 53.1 ± 13.8 ($p<0.00001$). Scores remained low through to 24 months follow up (16.8 ± 17.4 points) but then increased at 36 months follow up (27.9 ± 21.2 points) The decrease in fear of hypoglycaemia was correlated to the HYPO score ($r=0.47$ $p=0.010$), the Lability Index ($r=0.56$ $p=0.0007$), and insulin requirement ($r=0.69$) $p=0.000002$).	**None reported.**	Outcomes assessed using the Health Utilities Index mark 2 (HUI2) questionnaire and the hypoglycaemia fear survey (HFS). HUI2 assesses 6 attributes and provides a score from -0.03 worst possible health to 1.0 perfect health. The HFS has 23 questions with higher scores indicating a greater fear of hypoglycaemia. Overall questionnaire response rate was 68% among transplanted patients and 60% amongst controls. Patient in the two groups had similar HUI2 scores at baseline, however HFS scores were significantly higher in the transplanted group than the control group at baseline 53.1 ± 13.8 Vs 35.8 ± 15.6 ($p<0.000001$) Outcomes are not reported systematically, and comparison between transplant and control groups is seldom analysed. Selection of patients for transplant was mad eon the basis of hypoglycaemic events.

Ryan EA (2005)[3] *Five-year follow-up after clinical islet transplantation* **Case series** North America Study period: not stated **n = 65** Population: patients with type 1 DM and with at least one primary diabetes-related indication: • Severe recurrent hypoglycaemia (80%) • Severe glycaemic liability (60%) Mean age: 43 years (± 1.2) Female: 57% Technique: islet transplantation alone. Edmonton protocol: Glucocorticoid-free IS (usually daclizumab and sirolimus with tacrolimus) given orally. **Median follow-up: 36 months (range: 4-68 months)** • 1-year follow-up: n = 12 • 2-year follow-up: n = 13 • 3-year follow-up: n = 1 • 4-year follow-up: n = 5 • 5-year follow-up: n = 2 Conflict of interest: none stated	**Insulin requirements** • Insulin independence (no use of exogenous insulin for 4 weeks): 68% (44/65) • Completed procedure (received a set amount of islet equivalents with no insulin independence: 5% (3/65) • Insulin independence for ≥ 1 month: 94% (44/47 patients who completed the islet transplantation, median follow-up of 35.5 months) • Median duration of insulin independence: 15 months • Median duration of C-peptide secretion (indicating graft function): 25.2 months • Despite persistent graft survival, the majority of patients had to resume insulin therapy in order to maintain good glycaemic control Of patients who still required insulin (number not reported): • those who lost all graft function (measured by undetectable C-peptide levels), required more insulin than before the procedure • those who had persisting C-peptide secretion required significantly less insulin than before the procedure. **Hypoglycaemic episodes** (numbers not reported) • Hypoglycaemic score (yearly assessment of problematic hypoglycaemia) and lability index (yearly assessment of variability of blood glucose level) showed marked improvement after transplantation. • With the use of insulin there have been some episodes of hypoglycaemia and more lability, but the scores remain significantly improved for up to 4 years compared with values before transplantation. **Blood glucose control** o HbA_{1c} rose once graft functions was lost • HbA_{1c} was well controlled (6.4%) in subjects who remained insulin independent and those who were required insulin but who were C-peptide positive (6.7%) • HbA_{1c} was poorly controlled (9%) in patients who lost all graft function **Infusions** • 1 infusion: 3% (2/65) • 2 infusions: 80% (52/65) • 3 infusions: 17% (11/65)	**Acute complications** (of total patient group n = 65) • Major bleed related to procedure requiring intervention: 15 (23%) (7 required blood transfusion and 2 required laparotomy) • Portal vein thrombosis treated with anticoagulation and with no clinical sequelae: 5 (8%) • Gall bladder puncture that resolved with conservative management: 2 (3%) • In the longer term, changes consistent with fatty liver seen in 8 or 36 patients who had MRI after the procedure **IS therapy complications** (numbers not reported) • Mouth ulcers: 89% (2 cases of severe ulcers) • Diarrhoea: 60% • Acne: 52% • Edema: 43% (severe edema requiring change of IS regimen in 12%) • Pneumonia: 3 patients (percentage not reported)	Outcome of 18 patients was not reported. It is assumed that they did not complete the procedure.

Abbreviations used: DM, diabetes mellitus; DQoL, diabetes quality of life; HSQ,Health Status Questionnaire; IS, immunosuppressive; MRI, magnetic resonance imaging.			
Study details	**Key efficacy findings**	**Key safety findings**	**Comments**
Bucher P (2004)[5] *Morbidity associated with intraportal islet transplantation* **Case series** Switzerland Study period: 1992-2003 **n = 51** **(16 autotransplantations also reported)** Population: patients with type 1 DM. Technique: intraportal islet allotransplantations: 62 percutaneous transhepatic injections and 15 infusions by laparotomy during simultaneous islet–kidney transplantation (n = 15). **Follow-up: not stated** Conflict of interest: none stated	None reported	Islet infusions by laparotomy during simultaneous islet–kidney transplantation were done without complication. Percutaneous transhepatic injections: • 2 portal branch thrombosis (resolved with anticoagulation therapy) • 7 intra-abdominal hemorrhages (in 4 patients who all required transfusion) • Complications occurred only after percutaneous islet infusion ($p < 0.03$).	Allogeneic transplant procedures were performed either as simultaneous islet and kidney transplantations, as islet after kidney or as islet transplantation alone. Study reports procedural outcomes only (not long-term).

Abbreviations used: DM, diabetes mellitus; DQoL, diabetes quality of life; HSQ,Health Status Questionnaire; IS, immunosuppressive; MRI, magnetic resonance imaging.

Study details	Key efficacy findings	Key safety findings	Comments
Shapiro AM (2006)[2] *International trial of the Edmonton protocol for islet transplantation* **Case series** International (six North American centres, three European centres) Study enrolment period: May 2001-Jan 2003 **n = 36** Population: patients with type 1 DM and with at least one primary diabetes-related indication: • Severe recurrent hypoglycaemia (97%) • Severe glycaemic liability (56%) Mean age: 41 years Technique: islet transplantation alone Edmonton protocol: glucocorticoid-free IS (usually daclizumab and sirolimus with tacrolimus) given orally **Median follow-up: 41 months (range 37-50 months)** 2-year follow-up (n = 35) ≥3-year follow-up (n = 21) Conflict of interest: none stated	**Insulin requirements** • Insulin independence (freedom from need to take insulin and adequate glycaemic control) at any time during follow-up: 58% (21/36) Of these patients: • 16 (76%) were insulin dependent again at 2 years • 5 (14%) remained insulin independent at 2 years **Insulin requirements and graft function at 1 year follow-up** • Insulin independence with adequate glycaemic control: 44% (16/36) • Partial graft function (detection of C-peptide but no insulin independence): 28% (10/36) • Complete graft loss (initial detection of C-peptide): 28% (10/36) **Hypoglycaemic episodes** • All patients with residual graft function were protected from hypoglycaemic episodes (follow up ranging from 28 to 365 days after transplantation). **Infusions** • 1 infusion: 31% (11/36) • 2 infusions: 25% (9/36) • 3 infusions: 44% (16/36)	**Serious adverse events (n = 38)** • 23 were related to study therapy • Immunosuppression-related events included: neutropenia (5 cases), gastrointestinal conditions (2 cases) pneumonia, mouth ulcers, fever (number not stated) **Procedure-related events:** • Acute intraperitoneal bleeding: 9% (7/77 infusions) requiring blood transfusion (4 cases) or laparotomy (1 case) • Laparatomy for bile leak (1) • Severe hypoglycaemia in patient with primary graft nonfunction (1) • Partial branch-vein occlusions: 6% (2/36) requiring anticoagulation treatment **Nonserious adverse events (five most common)** • Mouth ulceration: 92% • Anaemia: 81% • Leukopenia: 75% • Diarrhoea: 64% • Headache: 56% Nine patients (25%) were switched to a non-sirolimus-based IS regimen due to side-effects. Mild hepatic steatosis (MRI) 2 years after transplantation: 31% (4/13 subjects followed up).	Likely to be the same patients as those reported in Ryan EA (2005).[3]

Abbreviations used: DM, diabetes mellitus; DQoL, diabetes quality of life; HSQ,Health Status Questionnaire; IS, immunosuppressive; MRI, magnetic resonance imaging.

Study details	Key efficacy findings	Key safety findings	Comments
Poggiolo R (2006)[4] *Quality of life after islet transplantation* **Case series** USA Study period: Nov 1996-Nov 2004 **n = 23** Population: patients with type 1 DM Females: 57% Mean age: 41 years (± 9 years) Technique: islet transplantation alone (n = 18) or islet after kidney transplantation (n = 5) **Follow-up: 3 years** Conflict of interest: none stated	*Outcomes assessed by questionnaire at baseline, 3 and 6 months after first infusion, and 3, 6, 9, 12, 18, 24, 30, and 36 months after protocol completion.* **DQoL score** • 12 months after protocol completion all DQoL scales, (satisfaction, impact and worry) had significantly improved from baseline ($p < 0.001$, $p < 0.001$ and $p = 0.003$ respectively). • Impact scale significantly improved at all follow-up time points compared with baseline. • Satisfaction and worry scales significantly improved at selected time points (3, 6, and 12 months after protocol completion) compared with baseline. • Re-introduction of insulin had a significant negative impact on satisfaction and impact scales ($p = 0.016$ and $p = 0.0007$ respectively). • Occurrence of adverse events and signs of graft dysfunction did not negatively alter DQoL scores. **HSQ 2.0 score** • Of all eight scales, only the health perception scale significantly improved at most time points compared with baseline ($p < 0.05$). • No other scales of this questionnaire changed significantly between baseline and follow-up except mental health which improved at 18 months after protocol completion ($p = 0.031$).		DQoL has 46 items assessing a broad range of diabetes-specific quality of life issues. Scales are: impact (of treatment on quality of life), satisfaction (with treatment) and worry (about future effects of diabetes and social issues). HSQ 2.0 has 8 scales and 36 questions assessing generic health-related quality of life. It is derived from the Short Form Health Survey (SF-36). Scales are: health perception, physical function, physical health, emotional problems, social function, mental health, bodily pain and energy/fatigue. Raw scores were included in the publication (as well as p-values). However, these haven't been listed here due to space constraints.

Abbreviations used: DM, diabetes mellitus; DQoL, diabetes quality of life; HSQ,Health Status Questionnaire; IS, immunosuppressive; MRI, magnetic resonance imaging.			
Study details	**Key efficacy findings**	**Key safety findings**	**Comments**
Hafiz MM (2005)[6] *Immunosuppression and procedure-related complications in 26 patients with type 1 diabetes mellitus receiving allogeneic islet cell transplantation* **Case series** USA April 2000-June 2004 **n = 26** Population: patients with type 1 DM Technique: • Islet after kidney transplantation = 4 • Islet transplantation alone = 16 • Islet transplantation alone plus infusion of CD34+ enriched bone marrow from same donor = 6 • Laparoscopic islet infusion = 1 IS regimen: steroid-free. Induction with daclizumab, maintenance with tacrolimus, sirolimus and in some cases, infliximab. **Follow-up: 22 months (± 11 months)** Conflict of interest: none stated	Not reported	**Serious adverse events (total = 27)** • Deaths: 0 • Life-threatening: 13/27 (48%) • With sequelae or persistent disability: 1/27 (4%) • Events relating to islet infusions: 4/27 (15%) • Events relating to IS regimen: 18/27 (66%) • Patients with 1 serious adverse event: 14/26 (54%) • Patients with ≥ 3 serious adverse events: 4/26 (15%) **Procedural complications** • Bleeding: 3/26 (12%) • Subacute cholecystitis: 1/26 (4%) • Abdominal hernia in 1 patient (4%) who had laparoscopic procedure • No cases of portal vein thrombosis **Most common post-procedural adverse events** ***Haematologic*** • Leucopenia: 100% (26/26) (6 patients required medication) • Anaemia: 96% (25/26) • Thrombocytopenia (mild and later normalised): 62% (16/26) • 1 patient with intermittent rash and itching had eosinophilia at 10 months after the procedure and was withdrawn from IS regimen ***Metabolic and liver function*** • Hypophosphatemia: 25/26 (96%) • Increased total cholesterol: 22/26 (85%) • Increased low density lipoprotein requiring medication or increased dosage of current medication: 20/26 (77%) • Increased triglycerides: 18/26 (69%) • Hypomagnesemia: 18/26 (69%) ***Neurological complications*** • Insomnia: 14/26 (54%) • Headaches: 12/26 (46%) • Fatigue: 8/26 (31%) • 2 patients (8%) developed severe tacrolimus neurotoxicity at 10 and 21 months after the procedure and required conversion to an	This study included simultaneous islet and kidney transplants and simultaneous islet and bone marrow transplantations. Each procedure may have a different safety profile which is not shown here since the results are combined for the treatment groups.

		alternative IS regimen • 1 patient developed insomnia, panic attacks and severe depression 6 months after the procedure and IS therapy eventually had to be withdrawn **Other complications** • Oral ulcerations: 20/26 (77%) • Upper respiratory infection: 18/26 (69%) • Diarrhoea: 18/26 (69%) • Ovarian cyst: 9/15 women (60%) • Vomiting: 12/26 (46%) • Nausea: 11/26 (42%)	

Abbreviations used: DM, diabetes mellitus; DQoL, diabetes quality of life; HSQ,Health Status Questionnaire; IS, immunosuppressive; MRI, magnetic resonance imaging.			
Study details	**Key efficacy findings**	**Key safety findings**	**Comments**
Molinari M (2005)[7] *Sirolimus-induced ulceration of the small bowel in islet transplant recipients: report of two cases* **Case report** Canada **n = 2** Population: patients with type 1 DM Case 1: 49-year old woman who had transplant in April 2001 Case 2: 40-year old woman who had transplant in Dec 2003 Technique: pancreatic islet cell transplantation with IS regimen of sirolimus **Follow-up: not reported** Conflict of interest: none stated		Case 1: insulin independence was achieved after a second transplant 4 months after the first. Ten weeks after second transplant, multiple aphthous oral ulcers and an ulcer of the ileum were found. It emerged that the patient was taking verapamil for migraine prophylaxis. Sirolimus was discontinued permanently and IS regimen was changed to tacrolimus only. The patient remained insulin independent 1 year post transplant and ulcers healed. Case 2: insulin independence was achieved after a second transplant 2 months after the first. Three weeks after the second transplant, several small mouth ulcers and a mucosal ulceration beyond the terminal ileum were found. Sirolimus was discontinued and IS regimen was modified to tacrolimus and mycophenolate mofetil for 3 weeks until symptoms resolved completely. The patient was restarted on low-dose sirolimus and tacrolimus. The patient remained insulin independent and the ulcer had resolved completely at follow-up 1 month after the ulcer was found.	

Abbreviations used: DM, diabetes mellitus; DQoL, diabetes quality of life; HSQ,Health Status Questionnaire; IS, immunosuppressive; MRI, magnetic resonance imaging.			
Study details	**Key efficacy findings**	**Key safety findings**	**Comments**
Barshes NR (2006)[8] *West Nile virus encephalopathy following pancreatic islet transplantation* **Case report** USA **n = 1** Population: 45-year old woman who underwent pancreatic islet transplantation 3 years earlier for type 1 DM Technique: pancreatic islet cell transplantation with various IS regimens including sirolimus and tacrolimus. **Follow-up: 3 years** Conflict of interest: none stated		The patient presented with fever and severe headaches. Lumbar puncture results were consistent with viral meningitis. IS medication was withheld and antibiotics were administered. The patient's condition deteriorated and changes suggestive of encephalitis were seen on electroencephalogram. The patient died soon afterwards. Enzyme-linked immunoassay results subsequently confirmed West Nile virus.	

Validity and generalisability of the studies

- A large number of studies were identified in the updated literature search for this procedure. Studies were only included in the overview if they assessed insulin independence, avoidance of hypoglycaemic episodes or some other measure of glycaemic control, or if they reported important safety outcomes.
- Different immunosuppression regimens were used in some studies.

Specialist advisers' opinions

Specialist advice was sought from consultants who have been nominated or ratified by their Specialist Society or Royal College.

Mr Chris Watson, Dr James Shaw, Professor Derek Gray, Professor Stephanie Amiel, Dr Martin Press, Professor Mike Nicholson, and Mr Adam Barlow

Safety

- Specialist Advisers stated that theoretical adverse events included transmission of donor material containing infectious agents or neoplastic cells; haemorrhage (from portal vein puncture); portal vein thrombosis; portal hypertension, complications resulting from immunosuppression such as mouth ulcers, infections, nephrotoxicity, deterioration in renal function; risk of primary failure of islets to function; continued problems with hypoglycaemia; risk of late loss of islet function; and immunisation against human histocompatibility antigens (implications for future transplants).
- One Specialist Adviser stated that the main adverse events associated with the procedure are directly related to the immunosuppression regimen (such as mouth ulcers, which are a major risk with sirolimus). There is also no clear consensus on the most appropriate immunosuppressive regime, and new regimes are under investigation.
- A major uncertainty was whether the long term adverse effects of the immunosuppresive regime outweighed the benefits in terms of diabetic control and complications.
- Anecdotal adverse events reported by Specialist Advisers included mouth ulcers, gastrointestinal disturbance, peripheral oedema, opportunistic infection, malignancy, hypertension, hyperlipidaemia, and sensitisation to transplantation antigens.
- One Specialist Adviser stated that there has been a report of one immunosuppressive-related death from Geneva.
- Most Specialist Advisers stated that the procedure has a better safety profile than whole pancreas transplantation.

Efficacy

- Specialist Advisers stated that key efficacy outcomes included insulin independence, improved glycaemic control (glycated haemoglobin levels), reduced incidence of hypoglycaemic episodes or reversal or

hypoglycaemic unawareness, and C-peptide levels (as an indicator of graft function in patients who remain on exogenous insulin).
- All but one Specialist Adviser stated that the main uncertainty in regard to the efficacy of this procedure is the long-term benefit in both in terms of graft function and diabetic complications such as neuropathy and retinopathy.
- One Specialist Adviser stated that a major uncertainty is the method of isolating and preparing islets. Another stated that often two transplants are needed because insufficient islets survive the transplant, which is an inefficient use of the donor pancreases.

Training
- One Specialist Advisers stated that the majority of the training and facilities required are involved with the isolation of islets from donor pancreas. This requires a purpose built accredited laboratory. The islet isolation is perhaps the most challenging part of the procedure, and also has a significant impact on the outcome. Another Specialist Adviser stated that the best method of isolating and preparing islets is a major uncertainty.
- The procedure requires interventional radiologists competent in percutaneous portal vein cannulation and for clinicians experienced in the use of immunosuppressive medications.

Other Specialist Advice
- Most Specialist Advisers commented that patient selection was important and that currently the procedure should be considered for patients with poor glycaemic control who are at risk of injury or death related to this, and patients who have undergone kidney transplant and therefore are already taking on the risks of immunosuppression.
- The main comparators were considered to be insulin pump therapy or whole pancreas transplantation for selected patients (who suffer repeated life-threatening hypoglycaemic episodes).
- One Adviser stated that it is generally agreed that there is no place for simultaneous islet and kidney transplantation since simultaneous pancreas and kidney transplantation is of proven efficacy.
- Most Specialist Advisers stated that the procedure would have a minor impact on the NHS and fewer than 10 centres would carry it out.

Issues for consideration by IPAC

- Criteria for optimal patient for selection for allogeneic pancreatic islet cell transplantation are not yet determined. However, it may be particularly indicated for diabetic patients who have recurrent severe hypoglycaemia or patients who are already undergoing immunosuppression (IS) for previous kidney transplantation.
- The studies in Table 2 have short-term follow-up and the Specialist Advisors stated that long-term efficacy of this procedure is a major uncertainty.

- Auto-transplantation (homologous) of pancreatic islet cells is also possible, usually in the context of an elective pancreatectomy. This overview does not cover this procedure.

References

1 Close N, Alejandro R, Hering B et al. (2007) Second annual analysis of the collaborative islet transplant registry. *Transplantation Proceedings* 39: 179-182.

2 Shapiro AM, Ricordi C, Hering BJ et al. (28-9-2006) International trial of the Edmonton protocol for islet transplantation.[see comment]. *New England Journal of Medicine* 355: 1318-1330.

3 Ryan EA, Paty BW, Senior PA et al. (2005) Five-year follow-up after clinical islet transplantation. *Diabetes* 54: 2060-2069.

4 Poggioli R. (2006) Quality of life after islet transplantation. *American Journal of Transplantation* 6: 371-378.

5 Bucher P. (2004) Morbidity associated with intraportal islet transplantation. *Transplantation Proceedings* 36: 1119-1120.

6 Hafiz MM, Faradji RN, Froud T et al. (27-12-2005) Immunosuppression and procedure-related complications in 26 patients with type 1 diabetes mellitus receiving allogeneic islet cell transplantation. *Transplantation* 80: 1718-1728.

7 Molinari M, Al Saif F, Ryan EA et al. (2005) Sirolimus-induced ulceration of the small bowel in islet transplant recipients: report of two cases. *American Journal of Transplantation* 5: 2799-2804.

8 Barshes NR, Agee EE, Zgabay T et al. (2006) West Nile virus encephalopathy following pancreatic islet transplantation. American Journal of Transplantation 6: 3037-3037.

9 Toso C, Shapiro JAM, Bowker S et al (2007) Quality of life after islet cell transplantation : impact of the number of islet transfusions and metabolic outcome. *Transplantation* 84: 664-667

Appendix A: Additional papers on allogeneic pancreatic islet cell transplantation for type 1 diabetes mellitus not included in summary Table 2

The following table outlines studies considered potentially relevant to the overview not included in the main data extraction table (Table 2). It is by no means an exhaustive list of potentially relevant studies.

Article title	Number of patients/ follow-up	Direction of conclusions	Reasons for non-inclusion in table 2
Badet, L., Benhamou, P. Y., Wojtusciszyn, A. et al (2007) Expectations and strategies regarding islet transplantation: metabolic data from the GRAGIL 2 trial. Transplantation 84 (1) 89-96.	n = 10 Follow-up: not reported	Insulin independence at 6 months: 60% Insulin independence at 12 months: 30% Successful metabolic control (based on 4 criteria) at 6 months: 60% Successful metabolic control at 12 months: 50%	Larger studies included in table 2
Barshes NR, Lee T, Goodpasture S et al. (2004) Achievement of insulin independence via pancreatic islet transplantation using a remote isolation center: a first-year review. *Transplantation Proceedings* 36: 1127-9.	n = 11 Follow-up: not stated in abstract	Insulin independence to date: 6/11 Decreased HA_{1c} levels: 11/11 No major complications related to procedure or IS regimen.	
Barshes NR, Lee TC, Goodpastor SE et al. (2005) Transaminitis after pancreatic islet transplantation. *Journal of the American College of Surgeons* 200: 353-61.	n = 11 Follow-up: not stated	Transaminitis after pancreatic islet transplantation is common (100%) and self-limited and does not signal acute rejection or serious procedure-related complications.	No outcomes of interest
Barshes NR, Goodpastor SE, Goss JA. (2003) Sirolimus-atorvastatin drug interaction in the pancreatic islet transplant recipient.[erratum appears in Transplantation (2004) 77: 328]. *Transplantation* 76: 1649-50.	n = 1 Follow-up: not stated	Drug interaction between sirolimus (IS therapy) and atorvastatin (antihypercholesterolemia) after transplantation. Elevated sirolimus trough levels so sirolimus dose reduced and no adverse effects were seen.	Larger studies included in table 2
Benhamou PY, Oberholzer J, Toso C et al. (2001) Human islet transplantation network for the treatment of type 1 diabetes: first data	n = 10 Follow-up: 12 months	0% primary graft nonfunction, 50% graft survival and 20% insulin-independence.	Larger studies included in table 2

from the Swiss-French GRAGIL consortium (1999-2000). Groupe de Recherche Rhin Rhne Alpes Geneve pour la transplantation d'Ilots de Langerhans.[see comment]. *Diabetologia* 44: 859-64.			
Berney T. (2004) Islet of Langerhans allogeneic transplantation at the University of Geneva in the steroid free era in islet after kidney and simultaneous islet-kidney transplantations. *Transplantation Proceedings* 36: 1121-2.	n = 8 (5 islet after kidney plus 3 simultaneous islet and kidney) Follow-up: 6 months (median)	100% functional grafts at follow-up. Of 5 patients who completed protocol, 4 became insulin independent. HbA_{1c} and fructosamine decreased over time, showing improved metabolic control. 4 severe adverse events. One simultaneous islet and kidney transplant patient died after treatment of severe kidney rejection	Larger studies included in table 2
Bertuzzi F, Grohovaz F, Maffi P et al. (2002) Successful [correction of Succesful] transplantation of human islets in recipients bearing a kidney graft. *Diabetologia* 45: 77-84.	n = 15 Follow-up: ≥ 1 year	No primary graft non-function. Insulin requirement reduced by > 50% in 14 patients. Insulin independence in 10 (66%) recipients, 5 of whom had prolonged insulin independence and well controlled fasting glycaemia (follow-up of 12 to 33 months).	Larger studies included in table 2
Close NC, Hering BJ, Eggerman TL. (2005) Results from the inaugural year of the Collaborative Islet Transplant Registry. *Transplantation Proceedings* 37: 1305–8.	n = 86 Follow-up: 8 months (mean)	At 6 months after the last infusion, 61.1% were insulin independent. At 12 months, 57.9% were insulin independent. No deaths and 45 serious adverse events reported to the registry.	More recent study from same registry included in table 2
Cretin N, Caulfield A, Fournier B et al. (2001) Insulin independence and normalization of oral glucose tolerance test after islet cell allotransplantation. *Transplant International* 14: 343–5.	n = 1 Follow-up: 3 years	Insulin independence 3 years after islet transplantation with normal oral glucose tolerance test (OGTT) (cured of diabetes).	Larger studies included in table 2
Cure P, Pileggi A, Faradji RN et al. (2006) Cytomegalovirus infection in a recipient of solitary allogeneic islets [4]. *American Journal of Transplantation* 6: 1089–90.	n = 1 Follow-up: not stated	Onset of cytomegalovirus 24 months after first infusion. IS regimen was reduced resulting in clearance of virus.	Larger studies included in table 2
Davalli AM, Maffi P, Socci C et al. (2000)	n = 1	Insulin independence 4 years after islet after kidney transplant.	Larger studies

Insights from a successful case of intrahepatic islet transplantation into a type 1 diabetic patient. *Journal of Clinical Endocrinology & Metabolism* 85: 3847–52.	Follow-up: 4 years	Glycosylated haemoglobin levels were best at 2 years followed by progressive decline.	included in table 2
Eckhard M, Lommel D, Hackstein N et al. (2004) Disseminated periportal fatty degeneration after allogeneic intraportal islet transplantation in a patient with type 1 diabetes mellitus: a case report. *Transplantation Proceedings* 36: 1111–6.	n = 1 Follow-up: not stated	Disseminated periportal fatty degeneration after allogeneic intraportal islet transplantation possibly due to steroid-free immunosuppression with rapamycin and tacrolimus.	Larger studies included in table 2
Eliaschewitz FG, Aita CA, Genzini T et al. (2004) First Brazilian pancreatic islet transplantation in a patient with type 1 diabetes mellitus. *Transplantation Proceedings* 36: 1117–8.	n = 1	No abstract available	Larger studies included in table 2
Frank A, Deng S, Juang X et al. (2004) Transplantation for type 1 diabetes. Comparison of whole-organ pancreas with isolated pancreatic islets. *Annals of surgery* 240: 631-643.	n = 43 (9 islet transplants alone, 4 islet after kidney transplants, 30 whole pancreas transplants) Follow-up: Not stated	<u>Islet transplantation</u> Insulin independence at any time: 11/12 Subsequent loss of graft function loss: 2/11 Resumed reduced insulin: 3/11 Insulin independence at 3 months to 2.5 years: 5/11 No hypoglycaemic episodes. 1 case of mouth ulcers, withdrawal of IS and graft failure <u>Whole pancreas transplantation</u> Continued functioning grafts: 83% (25/30) Lost graft function or death: 17% (5/30) 1 death (11 days after transplant) 2 cases of vascular thrombosis 2 cases of infection	Larger studies included in Table 2
Froud T, Ricordi C, Baidal DA et al. (2005) Islet transplantation in type 1 diabetes mellitus using cultured islets and steroid-free immunosuppression: Miami experience. *American Journal of*	n = 16 Follow-up: 33 months (mean)	Insulin independence: • At any time: 14/16 (88%) (2 did not complete protocol due to adverse events) • At 1 year: 11/14 (79%) • At 33 (+/-6) months: 6/14 (43%) Chronic partial graft loss: 8/14	Larger studies included in table 2

Transplantation 5: 2037–46.		(57%) (likely immunological in nature).	
Froud T, Baidal DA, Ponte G et al. (2006) Resolution of neurotoxicity and beta-cell toxicity in an islet transplant recipient following substitution of tacrolimus with MMF. *Cell Transplantation* 15: 613–20.	n = 1 Follow-up: not stated	Neurotoxicity symptoms requiring substitution of tacrolimus with mycophenolate mofetil (MMF), resulting in complete symptom resolution over 9 months.	Larger studies included in table 2
Froud T, Faradji RN, Gorn L et al. (2007) Dapsone-induced artifactual a1c reduction in islet transplant recipients. *Transplantation* 83: 824–5.	n = 1 Follow-up: not stated	No abstract available	Larger studies included in table 2
Gonzalez MM, Alonso A, Briones R et al. (2005) Pancreas islet transplantation in patients with type 1 diabetes mellitus after kidney transplantation. [erratum appears in Transplant Proc. 2005 Jul-Aug;37(6):2894 Note: Navarro, A [added]; Castro, MJ [added]; Sola, E [added]; Aranda, J [removed]; De la Fuente, A [removed]]. *Transplantation Proceedings* 37: 1443–5.	n = 2 Follow-up: not stated	After transplant, 1 patient required occasional insulin; the other patient reduced dose by 50%. No further hypoglycaemic unawareness episodes. No transplant-related complications.	Larger studies included in table 2
Goss JA, Schock AP, Brunicardi FC et al. (2002) Achievement of insulin independence in three consecutive type-1 diabetic patients via pancreatic islet transplantation using islets isolated at a remote islet isolation center. *Transplantation* 74: 1761–6.	n = 3 Follow-up: 4, 3, and 0.5 months	Mean HbA1c has dramatically reduced in 2 patients. No hyperglycaemic or hypoglycaemic episodes since transplantation. No complications.	Larger studies included in table 2
Goto T, Tanioka Y, Sakai T et al. (2005) Successful islet transplantation from a single pancreas harvested from a young, low-BMI, non-heart-beating cadaver.	n = 1 Follow-up: not stated	Minimal insulin still required, but good glycaemic control. No hypoglycaemic episodes at 3 months. No complications.	Larger studies included in table 2

Transplantation Proceedings 37: 3430–2.			
Hafiz MM, Poggioli R, Caulfield A et al. (2004) Cytomegalovirus prevalence and transmission after islet allograft transplant in patients with type 1 diabetes mellitus. *American Journal of Transplantation* 4: 1697–702.	n = 29 Follow-up: 450 days	Positive pretransplantation cytomegalovirus status of recipients: 45%. Positive pretransplantation cytomegalovirus status of donors: 58%. No cytomegalovirus transmission, reinfection, reactivation or invasive disease was observed after transplantation.	Larger studies included in table 2
Hering BJ, Kandaswamy R, Ansite JD et al. (2005) Single-donor, marginal-dose islet transplantation in patients with type 1 diabetes.[see comment][erratum appears in JAMA. 2005 Apr 6;293(13):1594]. *JAMA* 293: 830–5.	n = 8 Follow-up: 1 year	Insulin independence and freedom from hypoglycaemia: 8/8. Insulin-independence for longer than 1 year: 5/8. Graft failure: 3/8 (preceded by subtherapeutic sirolimus exposure). No procedure- or IS-related adverse events.	Larger studies included in table 2
Hirshberg B, Rother KI, Digon BJ, III et al. (2003) Benefits and risks of solitary islet transplantation for type 1 diabetes using steroid-sparing immunosuppression: the National Institutes of Health experience.[see comment]. *Diabetes Care* 26: 3288–95.	n = 1 Follow-up: not stated		Larger studies included in table 2
Kessler L, Passemard R, Oberholzer J et al. (2002) Reduction of blood glucose variability in type 1 diabetic patients treated by pancreatic islet transplantation: interest of continuous glucose monitoring. *Diabetes Care* 25: 2256–62.	n = 6 Follow-up: not stated	Less frequent and less severe hypoglycaemia: 6/6. Insulin independence at 1 year: 3/6. 1 partial portal vein thrombosis and 1 intra-abdominal hemorrhage. Common transient mouth ulcers, diarrhoea, edema, hypercholesterolemia, weight loss.	Larger studies included in table 2
Kessler L, Passemard R, Oberholzer J et al. (2002) Reduction of blood glucose variability in type 1 diabetic patients treated by pancreatic islet transplantation: interest of continuous glucose monitoring. *Diabetes Care* 25:	n = 26 (10 connected to insulin pump; 9 had simultaneous pancreas and kidney transplant; 7 had islet after kidney transplant) Follow-up: 3 days	Use of subcutaneous continuous glucose monitoring system confirms that islet transplantation can be as efficient as pancreas transplantation in restoring good metabolic control and reducing blood glucose variability.	Larger studies included in table 2

2256–62.			
Keymeulen B. (2006) Correlation between beta cell mass and glycemic control in type 1 diabetic recipients of islet cell graft. *Proceedings of the National Academy of Sciences of the United States of America* 103: 17444–9.	n = 1 Follow-up: not stated	1-year metabolic control can be reproducibly achieved and standardised by cultured islet cell grafts with defined beta cell number.	Larger studies included in table 2
Lakey, J. R., Kin, T., Warnock, G. L., Shapiro, A. M. et al (2007) Long-term graft function after allogeneic islet transplantation. Cell Transplantation 16 (4) 441-446.	n = 2 Follow-up: 10 and 13 years	2 female patients under went simultaneous islet-kidney transplant. Patient 1: reasonable blood glucose control achieved for up to 6 years, but little clinical benefit at 10 years. Patient 2: sustained insulin secretion with nearly normal HbA1c at 13 years.	Larger studies included in table 2
Langer RM, Mathe Z, Doros A et al. (2004) Successful islet after kidney transplantations in a distance over 1000 kilometres: Preliminary results of the Budapest–Geneva collaboration. *Transplantation Proceedings* 36: 3113–5.	n = 3 Follow-up: 7 months, 4 months, 2 weeks	1 patient achieved insulin independence and 2 patients had decreased requirements.	Larger studies included in table 2
Lehmann R. (2004) Successful simultaneous islet–kidney transplantation using a steroid-free immunosuppression: Two-year follow-up. *American Journal of Transplantation* 4: 1117–23.	n = 9 Follow-up: 2 years (median)	5 out of 6 patients with ≥ 2 islet transplantations became insulin independent. Mean post-transplantation HbA_{1c} level: 6.2% (8.7% prior to transplant).	Larger studies included in table 2
Maleux G, Gillard P, Keymeulen B et al. (2005) Feasibility, safety, and efficacy of percutaneous transhepatic injection of beta-cell grafts. *Journal of Vascular & Interventional Radiology* 16: 1693–7.	n = 15 Follow-up: not stated	Transient abdominal pain immediately after procedure: 3/15. Mean 3.8-fold increase in liver aminotransferase levels measured in all recipients 3 weeks after the first infusion. Functioning graft at 6 months: 13/15 (86%).	Larger studies included in table 2
Markmann JF, Deng S, Huang X et al. (2003) Insulin independence following isolated islet transplantation and single islet infusions.[see comment]. *Annals of*	n = 7 Follow-up: not stated	Insulin independence: 7/7. Subsequent graft function loss to date: 1/6 (patient suffered recurrent hyperglycemia 9 months after the transplant).	Larger studies included in table 2

Surgery 237: 741–9.			
Movahedi B, Keymeulen B, Lauwers MH et al. (2003) Laparoscopic approach for human islet transplantation into a defined liver segment in type-1 diabetic patients. *Transplant International* 16: 186–90.	n = 18 (laparoscopic approach) Follow-up: not stated	No efficacy outcomes reported. No surgical complications.	Larger studies included in table 2
Noguchi H, Iwanaga Y, Okitsu T et al. (2006) Evaluation of islet transplantation from non-heart beating donors. *American Journal of Transplantation* 6: 2476–82.	n = 5 (non-heart beating donors) Follow-up: not stated	Insulin independent: 3/5. Reduced insulin requirement: 2/5.	Larger studies included in table 2
O'Connell PJ, Hawthorne WJ, Holmes-Walker DJ et al. (2006) Clinical islet transplantation in type 1 diabetes mellitus: results of Australia's first trial. *Medical Journal of Australia* 184: 221–5.	n = 6 Follow-up: 2 years	Insulin-independence: 3/6. Reduced insulin requirement and no severe hypoglycaemia: 2/6. Graft function deteriorated over follow-up and insulin free patients required supplemental insulin. Complications: 1 postoperative bleed; 2 portal vein thromboses; 1 deterioration in renal function.	Larger studies included in table 2
Oberholzer J, Triponez F, Mage R et al. (2000) Human islet transplantation: lessons from 13 autologous and 13 allogeneic transplantations. *Transplantation* 69: 1115–23.	n = 13 (13 autotransplantations also reported) Follow-up: 3 months to 5 years	Insulin independence: 2/13 Graft failure: 6/13 HbA_{1c} decreased from 9.1% before transplantation to 5.5% at month 3.	Larger studies included in table 2
Okitsu T, Matsumoto S, Iwanaga Y et al. (2005) Kyoto islet isolation method: the optimized one for non-heart-beating donors with highly efficient islet retrieval. *Transplantation Proceedings* 37: 3391–2.	n = 6 Follow-up: not stated	Insulin independence: 2/6. Reduced insulin: 4/6. All recipients became free of hypoglycaemic episodes after transplantation and now have normal HbA_{1c} levels.	Larger studies included in table 2
Osama GA, Chamsuddin A, Fraga D et al. (2004) Insulin independence achieved using the transmesenteric approach to the portal vein for islet transplantation. *Transplantation* 77:	n = 3 Follow-up: Not stated	'The transmesenteric approach appears to be a safe alternative to percutaneous islet delivery. No complications.'	Larger studies included in table 2

309–11.			
Owen RJ, Ryan EA, O'Kelly K et al. (2003) Percutaneous transhepatic pancreatic islet cell transplantation in type 1 diabetes mellitus: radiologic aspects. *Radiology* 229: 165-170.	n = 34 (26 completed procedure) Follow-up: Not stated	Insulin independence: 26/26 Insulin independence at 1 year: 21/26 (81%) 3 subjects lost graft function Procedure-related complications: 13/68 procedures (19%) Serious complications: 6/68 (9%) 4 cases of bleeding 2 portal vein occlusions 4 biliary system punctures 2 vasovagal episodes	Larger studies included in table 2
Pattou F, Vantyghem MC, Noel C et al. (2000) Sequential intraportal islet allografts in immunosuppressed type I diabetic patients: preliminary results. *Transplantation Proceedings* 32: 391–2.	n = 1 Follow-up: not stated	Reduced insulin requirements 1 month after transplant.	Larger studies included in table 2
Paty BW, Ryan EA, Shapiro AM et al. (2002) Intrahepatic islet transplantation in type 1 diabetic patients does not restore hypoglycemic hormonal counterregulation or symptom recognition after insulin independence. *Diabetes* 51: 3428–34.	n = 7 Follow-up: not stated	Glucagon responses of islet transplant recipients to hypoglycaemia were significantly less than those observed in control subjects, and not significantly different from that of nontransplanted type 1 diabetic subjects.	Larger studies included in table 2
Paty BW, Senior PA, Lakey JR et al. (2006) Assessment of glycemic control after islet transplantation using the continuous glucose monitor in insulin-independent versus insulin-requiring type 1 diabetes subjects. *Diabetes Technology & Therapeutics* 8: 165–73.	n = 24 8 insulin-independent subjects after islet transplantation. 8 subjects who were C-peptide-positive but insulin-requiring after islet transplantation. 8 non-transplanted diabetic subjects. Follow-up: not stated	Continuous glucose monitoring system demonstrates that glycaemic lability and hypoglycaemia are significantly reduced in C-peptide-positive islet transplant recipients, whether or not supplementary, exogenous insulin is used, compared with non-transplanted type 1 DM subjects.	Larger studies included in table 2

Rickels, M. R., Kamoun, M., Kearns, J. et al (2007) Evidence for allograft rejection in an islet transplant recipient and effect on beta-cell secretory capacity. Journal of Clinical Endocrinology & Metabolism 92 (7) 2410-2414.	n = 1 Follow-up: not reported	42-yr-old woman with kidney and islet transplant IS was discontinued at 4 months for colitis. 6 months later she became insulin dependent again. Islet graft loss coincided with donor human leukocyte antigen sensitisation.	Larger studies included in table 2
Ryan EA, Lakey JR, and Shapiro AM. (2001) Clinical results after islet transplantation. *Journal of Investigative Medicine* 49: 559–62.	n = 12 Follow-up: ≤ 20 months	Insulin independence at any time: 12/12. During follow-up: 2 patients had hypoglycaemia episodes and now require insulin. Complications: • Transient rise in liver function tests (3) • Fatty infiltration in liver (1) • Portal vein thrombosis (1) • Bleeding requiring transfusion (2).	Larger studies included in table 2
Ryan EA, Lakey JR, Rajotte RV et al. (2001) Clinical outcomes and insulin secretion after islet transplantation with the Edmonton protocol. *Diabetes* 50: 710–9.	n = 12	Same results as reported above.	Larger studies included in table 2
Ryan EA (2002) Successful islet transplantation: Continued insulin reserve provides long-term glycemic control. *Diabetes* 51: 2148–57.	n = 30 Follow-up: 1 year in 15 consecutive patients	Insulin independence at 1 year: 12/15 (80%). Stable glucose control, glycemic lability and no hypoglycemic episodes: 14/15. Complications: Portal vein thrombosis: 2/54 procedures. Bleeding: 5 subjects (4 transfusions). Transient elevated liver function tests: 46%.	Larger studies included in table 2
Ryan EA, Shandro T, Green BW (2004) Assessment of the severity of hypoglycemia and glyceemic lability in type 1 diabetic subject undergoing islet transplantation. *Diabetes* 53: 955-962.	n = 51 Follow-up:1 month	Article focuses on testing a scoring system for hypoglycaemia and glycaemic lability. Patients are most likely the same as those reported in Ryan et al 2005 study in table 2	
Ryan EA, Shapiro AJ (2006) A patient with severe, recurrent hypoglycemia and glycemic lability who underwent islet transplantation. *Nature Clinical Practice*	n = 1 Follow-up: not stated	Hypoglycaemia abated and excellent stable glycaemic control attained after transplant. Deterioration in graft function requiring reinstitution of (lower dose) insulin 2.5 years after transplant. Occasional hypoglycaemic episodes and	Larger studies included in table 2

Endocrinology & Metabolism 2: 349–53.		some glycaemic lability have recurred, although endogenous insulin secretion is still preserved	
Shapiro AM, Lakey JR, Ryan EA et al. (2000) Islet transplantation in seven patients with type 1 diabetes mellitus using a glucocorticoid-free immunosuppressive regimen. [see comment]. *New England Journal of Medicine* 343: 230–8.	n = 7 Follow-up: 12 months (median)	Sustained insulin independence: 7/7 Normal HbA_{1c} values: 7/7. No further episodes of hypoglycaemic coma. Complications were minor, and there were no significant increases in lipid concentrations during follow-up.	Larger studies included in table 2
Venturini M, Angeli E, Maffi P et al. (2005) Technique, complications an therapeutic efficacy of percutaneous transplantation of human pancreatic islet cells in type 1 diabetes: The role of US. *Radiology* 234: 617-624	n = 34 Follow-up Not stated	Insulin independence for > 3 months: 12/34 (35%) Mean duration of independence: 21 months ± 4.2 Reduced insulin requirements: 22/34 (65%) Early complications (3/58 procedures (5%)) 2 cases of bleeding 1 case portal vein thrombosis	Larger studies included in table 2
Warnock GL, Meloche RM, Thompson D et al. (2005) Improved human pancreatic islet isolation for a prospective cohort study of islet transplantation vs best medical therapy in type 1 diabetes mellitus. *Archives of Surgery* 140: 735–44.	n = 10 Follow-up: not stated	Daily insulin dependence was reversed in all patients for at least 3 months. Five patients resumed small insulin doses. Compared with the best-care programme, all patients had improved metabolic stability.	Larger studies included in table 2
Yakubovich N. (2007) Three cases of cytomegalovirus infection following pancreatic islet transplantation. *Transplantation Proceedings* 39: 1599–603.	n = 3 Follow-up: not stated	Three cases of cytomegalovirus infection following islet transplantation for type 1 diabetes despite prophylaxis with valganciclovir.	Larger studies included in table 2
Yang TY, Oh SH, Jeong IK et al. (2002) First human trial of pancreatic islet allo-transplantation in Korea – focus on re-transplantation. *Diabetes Research & Clinical Practice* 56: 107–13.	n = 1 Follow-up: not stated in abstract	After re-transplantation, glucose profile became more stable and episodes of severe hypoglycemia ceased.	Larger studies included in table 2

Appendix B: Related published NICE guidance for allogeneic pancreatic islet cell transplantation for type 1 diabetes mellitus

Guidance programme	Recommendation
Interventional procedures	**Pancreatic islet cell transplantation** 1.1 Current evidence on the safety and efficacy of pancreatic islet cell transplantation does not appear adequate to support the use of this procedure without special arrangements for consent and for audit or research. Clinicians wishing to undertake pancreatic islet cell transplantation should inform the clinical governance leads in their trusts. They should ensure that patients offered it understand the uncertainty about the procedure's safety and efficacy and should provide them with clear written information. Use of the Institute's Information for the Public is recommended. Clinicians should ensure that appropriate arrangements are in place for audit or research. Publication of safety and efficacy outcomes will be useful in reducing the current uncertainty. NICE is not undertaking further investigation at present. 1.2 All cases should be registered with the International Islet Transplant Registry, which is based in Germany and run by Mathias D Brendel, Third Medical Department, University Hospital Giessen, D-35385 Giessen, Germany (www.med.uni-giessen.de/itr/).
Technology appraisals	**Diabetes (type 1) insulin pump therapy** 1.1 Continuous subcutaneous insulin infusion (CSII or 'insulin pump therapy') is recommended as an option for people with type 1 diabetes provided that: • multiple-dose insulin (MDI) therapy (including, where appropriate, the use of insulin glargine) has failed; and • those receiving the treatment have the commitment and competence to use the therapy effectively. 1.2 People for whom MDI therapy has failed are considered to be those for whom it has been impossible to maintain a haemoglobin A1c level no greater than 7.5% (or 6.5% in the presence of microalbuminuria or adverse features of the metabolic syndrome) without disabling hypoglycaemia occurring, despite a high level of self care of their diabetes. 'Disabling hypoglycaemia', for the purposes of this guidance, means the repeated and unpredictable occurrence of hypoglycaemia requiring third-party assistance that results in continuing anxiety about recurrence and is associated with significant adverse effect on quality of life. 1.3 CSII therapy should be initiated only by a trained specialist team, which should normally comprise a physician with a specialist interest in insulin pump therapy, a diabetes specialist nurse and a

	dietitian. 1.4 All individuals beginning CSII therapy should be provided with specific training in its use. Ongoing support from a specialist team should be available, particularly in the period immediately following the initiation of CSII. It is recommended that specialist teams should agree a common core of advice appropriate for CSII users. **Diabetes (types 1 and 2) long-acting insulin analogues** 1.1 Insulin glargine is recommended as a treatment option for people with type 1 diabetes. 1.2 Insulin glargine is not recommended for routine use for people with type 2 diabetes who require insulin therapy. Insulin glargine treatment should be considered only for those people with type 2 diabetes who require insulin therapy and who fall into one of the following categories. • Those who require assistance from a carer or healthcare professional to administer their insulin injections. • Those whose lifestyle is significantly restricted by recurrent symptomatic hypoglycaemic episodes. • Those who would otherwise need twice-daily basal insulin injections in combination with oral antidiabetic drugs.
Clinical guidelines	**Type 1 diabetes** *Insulin regimens* 1.1 Adults with type 1 diabetes should have access to the types (preparation and species) of insulin they find allow them optimal well-being. 1.2 Cultural preferences need to be discussed and respected in agreeing the insulin regimen for a person with type 1 diabetes. 1.3 Multiple insulin injection regimens, in adults who prefer them, should be used as part of an integrated package of which education, food and skills training should be integral parts. 1.4 Appropriate self-monitoring and education should be used as part of an integrated package to help achieve optimal diabetes outcomes. 1.5 Meal-time insulin injections should be provided by injection of unmodified ('soluble') insulin or rapid-acting insulin analogues before main meals. 1.6 Rapid-acting insulin analogues should be used as an alternative to meal-time unmodified insulin: • where nocturnal or late inter-prandial hypoglycaemia is a problem • in those in whom they allow equivalent blood glucose control without use of snacks between meals and this is needed or desired. 1.7 Basal insulin supply (including nocturnal insulin supply) should be provided by the use of isophane (NPH) insulin or long-acting insulin analogues (insulin glargine). Isophane (NPH) insulin should be given at bedtime. If rapid-acting insulin analogues are given at meal times or the midday 1.8 insulin dose is small or lacking, the need to give isophane (NPH) insulin twice daily (or more often) should be considered. 1.9 Long-acting insulin analogues (insulin glargine) should be used when: • nocturnal hypoglycaemia is a problem on isophane (NPH)

	insulin • morning hyperglycaemia on isophane (NPH) insulin results in difficult daytime blood glucose control • rapid-acting insulin analogues are used for meal-time blood glucose control. 1.10 Twice-daily insulin regimens should be used by those adults who consider number of daily injections an important issue in quality of life. • Biphasic insulin preparations (pre-mixes) are often the preparations of choice in this circumstance. • Biphasic rapid-acting insulin analogue pre-mixes may give an advantage to those prone to hypoglycaemia at night. Such twice daily regimens may also help: • those who find adherence to their agreed lunch-time insulin injection difficult • adults with learning difficulties who may require assistance from others. 1.11 Adults whose nutritional and physical activity patterns vary considerably from day to day, for vocational or recreational reasons, may need careful and detailed review of their self-monitoring and insulin injection regimen(s). This should include all the appropriate preparations (see Sections 1.9.3.6–8), and consideration of unusual patterns and combinations. 1.12 For adults undergoing periods of fasting or sleep following eating (such as during religious feasts and fasts or after night-shift work), a rapid-acting insulin analogue before the meal (provided the meal is not prolonged) should be considered. 1.13 For adults with erratic and unpredictable blood glucose control (hyper- and hypoglycaemia at no consistent times), rather than a change in a previously optimised insulin regimen, the following should be considered: • resuspension of insulin and injection technique • injection sites • self-monitoring skills • knowledge and self-management skills • nature of lifestyle • psychological and psychosocial difficulties • possible organic causes such as gastroparesis. 1.14 Continuous subcutaneous insulin infusion (or insulin pump therapy) is recommended as an option for people with type 1 diabetes provided that: • multiple-dose insulin therapy (including, where appropriate, the use of insulin glargine) has failed;* and • those receiving the treatment have the commitment and competence to use the therapy effectively. 1.15 Partial insulin replacement to achieve blood glucose control targets (basal insulin only, or just some meal-time insulin) should be considered for adults starting insulin therapy, until such time as islet B-cell deficiency progresses further. 1.16 Clear guidelines and protocols (‘sick-day rules’) should be given to all adults with type 1 diabetes to assist them in adjusting insulin doses appropriately during intercurrent illness. 1.17 Oral glucose-lowering drugs should generally not be used in the management of adults with type 1 diabetes.

	Insulin delivery 1.18 Adults with diabetes who inject insulin should have access to the insulin injection delivery device they find allows them optimal well-being, often using one or more types of insulin injection pen. 1.19 Adults with type 1 diabetes who have special visual or psychological needs should be provided with injection devices or needle-free systems that they can use independently for accurate dosing. 1.20 Insulin injection should be made into the deep subcutaneous fat. To achieve this, needles of a length appropriate to the individual should be made available.

Appendix C: Literature search for allogeneic pancreatic islet cell transplantation for type 1 diabetes mellitus

Database	Date searched	Version/files
CRD databases (DARE & HTA)	23/07/2007	Issue 3, 2007
CENTRAL	23/07/2007	Issue 3, 2007
EMBASE	23/07/2007	1980 to 2007 Week 33
Medline	23/07/2007	1950 to August Week 3 2007
Premedline	23/07/2007	August 22, 2007
CINAHL	23/07/2007	1982 to August Week 3 2007
BLIC	23/07/2007	1993 to date
National Research Register	23/07/2007	2007, Issue 3
Controlled Trials Registry	23/07/2007	-

The following search strategy was used to identify papers in Medline. A similar strategy was used to identify papers in other databases.

1. exp "Islets of Langerhans Transplantation"/ (5815)
2. exp "Islets of Langerhans"/ (30092)
3. (islet$ adj2 langerhan$).tw. (3801)
4. (pancrea$ adj3 islet$).tw. (12080)
5. (beta adj2 cell$).tw. (26563)
6. or/2-5 (49372)
7. Cell Transplantation/ (4697)
8. Transplantation, Autologous/ (35388)
9. Transplantation, Homologous/ (62487)
10. Transplantation, Heterotopic/ (2864)
11. transplant$.tw. (226482)
12. or/7-11 (281016)
13. 6 and 12 (4698)
14. 1 or 13 (7477)
15. exp Pancreatitis, Chronic/ (448)
16. (pancrea$ adj3 chronic).tw. (10256)
17. exp Diabetes Mellitus, Type 1/ (46210)
18. (diabet$ adj3 mellitus adj3 (type 1 or second$)).tw. (4306)
19. or/15-18 (57257)
20. 14 and 19 (1655)
21. Animals/ (4180312)
22. Humans/ (9909878)
23. 21 not (21 and 22) (3168650)
24. 20 not 23 (1217)
25. limit 24 to yr="2000 - 2007" (621)
26. limit 25 to english language (572)